POPULATION STUDIES IN RISK ASSESSMENT: STRENGTHS AND WEAKNESSES - Margaret R. Becklake, McGill University, Montreal, Quebec. Canada.

Epidemiologic studies provide information on the distribution and determinants of health related events in populations. Use is made of whatever method or study design (prevalence, case control, cohort) is appropriate to the health related event in question, depending amongst other things on its nature, incubation time, and the certainty with which it is possible to establish a diagnosis. Exposure response relationships make an important contribution to establishing causality particularly when an environmental agent is under scrutiny. Applicability of the findings to risk assesment and to environmental standard setting, in the workplace or in the public health context, is directly related to the extent to which the environmental measurements used to characterize exposure are quantitative rather than qualitative.

Asbestos is a topical example to illustrate the strengths and weaknesses of population based information in this context. It is also one responsible for malignant as well as nonmalignant illhealth effects, thus challenging both molecular and experimental biology (to explain mechanisms) and epidemiology (to quantitative risk). For this agent, too, the epidemiologic data base is probably more extensive than for any other. Its major strength (and this is true for any population data base) is biologic: human data does not require account to be taken of species differences. In addition, many occupational exposures have been reasonably well characterized in terms of airbrone fibres or dust, and they usually involve definable populations whose health status can be directly assessed. Sample size, when limited to a particular workforce, may reduce sensitivity. Nevertheless workplace standards, reasonably broadly based, have been framed around the risk of developing pulmonary fibrosis (asbestosis). A weakness of the data base is its insensitivity at low levels of exposure. Nevertheless because there is almost no epidemiologic data on the health consequences to the general public of environmental exposure, eg. in schools or building, extrapolations from the occupational data base have been used for risk assessment to the public, the major concern being cancer. Alternative strategies, also epidemiologic, are however available for assessing the impact on the public's health, for instance monitoring sex trends in mesothelioma incidence, and these might also provide an approach to risk assessment.

HUMAN CLINICAL EXPOSURE STUDIES: BODY BOX OR PANDORA'S BOX - M.J. Utell, University of Rochester Medical Center, Rochester, NY 14642

Controlled clinical studies have provided a means for examining responses to air pollutants identified from epidemiologic studies. Typically, the exposures are performed in environmental chambers and the responses are assessed by indices of respiratory mechanics. To date, inhalation studies have identified general patterns of lung function response in specific subpopulations. Several observations from clinical studies will be discussed to illustrate the relevance of these findings. For example: 1) after inhalation of ozone, normal and asthmatics manifest equivalent reductions in lung volumes at similar pollutant concentrations. 2) With acute exposure to the soluble gas SO_2 or acidic sulfate particles, asthmatics may be an order of magnitude more sensitive than healthy adults and characteristically show changes in flow rates and airway resistance. 3) In contrast, following inhalation of the oxidant NO_2, responses have been less consistent and more difficult to characterize but have included both obstructive and restrictive changes in volunteers with underlying airways disease. In order to examine mechanisms of pollutant-induced toxicity, the technique of bronchoalveolar lavage has been introduced into controlled clinical studies. Endpoints studied to date have included influx of inflammatory cells, measurements of products of arachidonic acid metabolism, analysis of proteins and enzymes released by alveolar macrophages, and lavaged leukocyte antiviral activity. Recently, other approaches available in the clinical arena including nasal lavages and clearance rates of radiolabelled aerosols from the airway to the blood have been adapted to evaluate pollutant responses. Although the clinical study cannot monitor the development of chronic disease from exposure, data from the "body box" has impacted substantially on our understanding of acute pollutant-induced effects. Further efforts to characterize subpopulations at risk and examine mechanisms of response using pulmonary data from controlled pollutant studies are clearly warranted.

OCCUPATIONAL EXPOSURE STANDARDS IN EUROPE: HISTORY, PRESENT STATUS AND FUTURE TRENDS -

D. Henschler, Institute of Toxicology, University of Würzburg, Fed. Rep. Germany

The first exposure standards were published in Germany as early as 1886 by K.L. Lehmann. By 1938, more than 100 short- and long-term standards had been proposed. At present, Germany, the Netherlands and Sweden prepare their own lists of standards; some other countries who up to now have used the US TLV-List are now starting initiatives of their own. Although the legislative background differs widely, all lists have important general features in common: separation of scientific evaluation from political decisions; consideration of field experience as well as animal experimentation; handling of carcinogens as a special category; preparation of monographs to elucidate the background for setting individual standards.

The establishment of occupational exposure standards is based on the assumption that thresholds of toxic effects do exist. Some model cases to demonstrate the existence of a threshold have been published. Prerequisites for thresholds are: reversibility of the relevant toxic effect; reversal of the toxic effect must have zero order kinetics; on repeated exposure, a steady-state level of the occupational toxicant must be reached which is regarded as safe; sufficient knowledge about the mechanism of action must be available. Most standards are, however, based on insufficient empirical information. At present, new philosophies are being elaborated to create "safe" standards for some types of occupational carcinogens.

During the past two decades, some new entries into the lists of standards have been made: classification of occupational carcinogens, regulations for peak vs. time-weighted average exposures, applicability or inapplicability of standards for women of child-bearing age. Recently, the EEC has again tried to establish a common list for the European member states.

CURRENT APPROACHES FOR DETERMINING WORK PLACE EXPOSURE LIMITS IN THE USA -

T.R. Lewis, National Institute for Occupational Safety and Health, Cincinnati, OH 45226

Application of research findings to the development and support of work place exposure limits for chemical substances in the United States of America is performed by several organizations -- the Occupational Safety and Health Administration (OSHA), the Mine Health and Safety Administration (MSHA), the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH), the American National Standards Institute (ANSI), the American Society for Testing and Materials (ASTM), the American Industrial Hygiene Association (AIHA) and individual states. It is the function of OSHA and MSHA to promulgate legal standards. NIOSH has responsibility for developing criteria and making recommendations to OSHA and MSHA for the promulgation of legal standards. Individual states also promulgate standards which are legal within their respective jurisdictions. Recommendations by the other organizations, are not legally binding, but are often voluntarily assumed by industry and may be adopted as legal standards by regulatory agencies. Industries, in turn, also develop work place exposure limits for application to their particular facilities; this is particularly important when an industry is the sole manufacturer or user.

By contrast to certifying food additives, drugs and pesticides, there are no formalized testing requirements for determining the hazards from chemical substances used within the work environment. However, the key question to be addressed in determining occupational exposure limits is what levels pose significant hazards to health and what levels can be accepted without undue risk to health. Development of occupational exposure limits involves review and evaluation of available technical information on a chemical substance and publication of written documentation supporting a proposed exposure limit which then may be adopted by a sponsoring professional organization (ACGIH, AIHA, ANSI, ASTM) or promulgated into law by regulatory agencies.

CORRELATION OF CARCINOGENIC POTENCY ESTIMATED FROM ANIMAL AND HUMAN DATA - K.S. Crump, B.A. Allen, A.M. Shipp, K S Crump and Company/Clement Associates, Inc., Ruston, LA 71270

This study provides a detailed and systematic investigation of the correlation between estimates of carcinogenic potency derived from animal and human data. Chemicals included are all those for which suitable animal and human data could be located and for which there are strong indications that the chemical is carcinogenic in either animals or humans. Twenty-three chemicals were found to satisfy these criteria; these include thirteen industrial chemicals (for which exposures are primarily via inhalation), seven drugs, two food additives or contaminants, and tobacco smoke. The human data on each of these chemicals were used to calculate a carcinogenic potency and a corresponding range. The animal data were entered into a computer data base that permitted a wide range of analyses to be performed systematically. The analyses performed to date indicate a strong correlation between the animal and human results. These correlations are strongest when analyses are restricted to the higher quality animal data. These results indicate that estimates of human cancer risk can be reasonably based on animal data. They also provide information on the uncertainty in such estimates and on the most appropriate ways to extrapolate animal data to humans. The analysis approach that most nearly approximates that used by the U.S. Environmental Protection Agency appears generally to overestimate risk in humans from the chemicals in this analysis by about sevenfold.

OZONE REMOVAL IN THE NASOPHARYNX AND LUNGS OF NORMAL MAN DURING TIDAL BREATHING - J.J. O'Neil, T.A. Gerrity, R.A. Weaver, J.H. Berntsen, J.H. Overton, and F.J. Miller, Inhalation Toxicology Division, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, School of Public Health, University of North Carolina, Chapel Hill, NC 27514, and Environmenal Monitoring Services, Inc., Chapel Hill, NC 27514.

The purpose of this study was to determine the amount of ozone removed in the nasopharynx and lungs of normal volunteers in order to better estimate the actual dose of ozone delivered to pulmonary tissues. Respiratory gases in 18 young non-smoking male subjects were collected from the posterior pharynx through a French #8 polyethylene tube which was connected to a rapidly responding ozone analyzer. Ventilation was measured using the Respitrace (TM) inductance plethysmograph. Each subject was asked to breathe at one tidal volume during all measurements by targeting volumes which had been previously established during spontaneous resting breathing. Subjects employed three modes of breathing (oronasal, nasal, and oral) with two frequencies (12 and 24 breaths per minute [bpm]) and were exposed to three ozone concentrations (0.1, 0.2, or 0.4 ppm). Ozone removal in the supra-laryngeal airways was calculated from the concentration measured in the posterior oropharynx during inspiration and ozone removal by the lungs from the concentration measured in the posterior oropharynx during expiration. Significant, though small, differences were observed in the oronasal removal of ozone with 48.1±1.07%, 41.3±1.06% and 45.0±1.06% removed during oronasal, nasal, and mouth breathing, respectively. An average of 46.0±0.9% and 43.6±0.9% was removed at 12 and 24 bpm, respectively. Of the ozone which reached the posterior pharynx, the lungs removed 89.2±0.4% and 85.3±0.4%, respectively, at 12 and 24 bpm. While the differences in these data at each mode of breathing are probably of little physiological significance, they permit one to calculate the amount of ozone removed by the tissues and are similar to the values calculated using dosimetric models previously derived in this laboratory. It, thus, is possible to translate concentration-response curves to dose-response curves for mean changes of pulmonary function in man. This permits analysis of exposure patterns to be developed for assessment of health effects from exposure to ozone. This is a proposed presentation and does not necessarily reflect EPA policy.

1.

OZONE CONCENTRATION - RESPONSE RELATIONSHIP: IMPLICATIONS FOR STANDARD SETTING AND RISK ASSESSMENT. M.J. Hazucha, University of North Carolina at Chapel Hill, Center for Environmental Medicine, Medical Research Building C 224H, Chapel Hill, NC 27514

A detailed comparison of literature-reported averaged decrements in pulmonary function of normal subjects exposed to ozone has been undertaken. The data base was formed by including data published during the past 20 years, from studies which reported at least one of the pulmonary function variables (FVC, FEV_1, FEF_{25-75}, RAW), acquired at 2 hours of exposures utilizing either original or modified Bates-Hazucha (intermittent exercise) protocol, and satisfied selection criteria. The final set of data (24 studies involving 299 subjects), was divided by ventilation rate (exercise loads) into 4 categories: light, moderate, high, and very high ventilation level. For each variable (FVC, etc.) and ventilation level a quadratic function has been fitted to the data using regression procedures. The curve parameter estimates have been computed, tabulated and statistically evaluated. The slope (quadratic coefficient) for each variable within a group and almost all variables between groups were significantly different from zero and from each other at $p < 0.0001$ level. Very high regression coefficients ($r = 0.823 - 0.991$) makes the models acceptable for quantitative prediction(s) of pulmonary function decrement(s). Furthermore, the analyses show that neither "effective rate" (the product of minute ventilation and O_3 concentration), nor "effective dose" (the product of O_3 concentration, minute ventilation and exposure time) are valid concepts. Although individual studies, because of their inherent design limitations, might appear to support the validity of such calculations, a comprehensive evaluation of all data available does not confirm it. Further, a critical appraisal of the data base and derived models does not provide any convincing argument for the presence of a threshold, i.e. an O_3 concentration below which no (measurable) pulmonary function change occurs in group studies. Less reactive individuals might not show a measurable response below a certain exposure level, which could be interpreted as a threshold; however, the cummulative data best fit a continuous model. The introduction of a threshold into the tested models did not improve the fit, further supporting the arguments against the evidence of a relative threshold.

SHORT-TERM EXPOSURE EFFECT RELATIONSHIPS FOR OZONE: INFLUENCE OF CONCENTRATION, EXPOSURE TIME PER DAY AND DURATION OF EXPOSURE - P.J.A.Rombout, L.van Bree, J.A.M.A.Dormans, M.Marra and S.H.Heisterkamp, National Institute of Public Health and Environmental Hygiene, Department of Inhalation Toxicology, 3720 BA Bilthoven, The Netherlands.

A large discrepancy exists between the actual conditions of population exposure to ozone and the clinical exposures upon which health standards for ozone are mainly based. Actual ozone exposures to 80% of the maximum 1 h value may last 10-12 h per day for several consecutive days or weeks. Clinical studies typically use exposure times of ozone to three hours.
To investigate the possible health consequences of this discrepancy, rats were exposed to ozone under carefully controlled conditions to determine the relative influence of concentration, exposure time per day and exposure duration. The factors under scrutiny were quantitatively evaluated by increases in pulmonary antioxidant enzyme activities and bronchoalveolar protein accumulation. In addition, pulmonary morphological alterations were qualitatively evaluated. Exposure-response relationships were established for ozone concentrations of 150-1000 $\mu g/m^3$, exposure times of 2-24 h per day and exposure durations of 1-16 days.
Both concentration and exposure time per day had a very significant positive influence on the ozone-induced response whereas the contribution of exposure duration was only about half of that of exposure time.
Typically, ozone concentrations of 2-300 $\mu g/m^3$ caused significant biochemical and morphological alterations after continuous exposure for several days. Similar pulmonary alterations were observed after an 8 h exposure for the same duration to 800 $\mu g/m^3$.
In view of an adequate ozone health risk assessment these results support the need for clinical exposures with longer than usual exposure times and -durations. Moreover, these data favour the introduction of an additional lower ozone standard with a longer averaging time (e.g. 8 h) and/or an appropriate reduction of the present 1 h standards.

PULMONARY FUNCTION TESTS IN THE RISK ASSESSMENT OF THE EFFECTS OF AMBIENT OZONE: AN ADVERSE HEALTH EFFECT OR A NEUROMEDIATED REFLECTORIC RESPONSE? - J. J. Vostal, General Motors Research Laboratories, Warren, MI, U.S.A.

A growing body of experimental evidence documents that respiratory airways and lung parenchyma are the targets for injury due to high concentrations of ozone. Minimal changes in pulmonary function only are produced by low ambient concentrations (≤ 0.3 ppm) of ozone that are not detected by epidemiology or animal experiments and can be observed solely in controlled human exposures. Minor decreases in peak respiratory flow rates, reported in children during summer camp activities, suffer from large variability of individual measurements. In view of significant confounding factors, such as clima or learning effects (Lioy et al., 1985), the field studies remain unconvincing. In addition, the forced expiratory volume decrements found after 0.2 ppm ozone in controlled human exposures do not represent on the average more than 4-5% of the 1-sec exspiratory volume (FEV_1) even after the heaviest exercise (U.S. EPA, 1986). The physiological significance of these changes is uncertain since both the narrowing of the airways as well as the inhibition of maximal inspiration, whether voluntary (due to discomfort) or involuntary (due to reflex pathways), are mediated by neural stimulation rather than by a direct effect of ozone on the sensitive respiratory airways. Pretreatment with atropine prevents an increase in airways resistance and partially blocks a decrease in FEV_1 (Beckett et al., 1985). The observed decrement in pulmonary function tests must be, therefore, interpreted as a transient stimulation of the airways' vagal receptors which does not have the character of an adverse health effect and cannot serve as a scientific basis for meaningful air quality regulations. Inter-individual differences in the sensitivity of nervous receptors also explain why some fraction of tested subjects ("responders") show greater than 10% reduction in FEV_1 after exposures to 0.12 ozone (McDonnell et al., 1983) and oppose the assumption that the responders represent a specific population subgroup. Recent animal experiments support the negative findings at near-ambient ozone levels since no permanent changes occur after continuous long-term exposures unless the concentrations are as high as 0.6-0.7 ppm (Gross and White, 1985, Wright et al., 1986); i.e. levels nearly twice as high as the highest reported ambient ozone concentrations.

CATEGORY E
RISK ASSESSMENTS FOR AIRBORNE TOXICANTS
POSTERS

Exposure to MMMF in the indoor non-occupational environment - G.R. Lundqvist, Institute of Hygiene, Universitetsparken Bygning 180, DK-8000 Aarhus C, Denmark

The presence of man-made mineral fibres (MMMF) in the indoor non-occupational environment has been connected with the occurence of acute discomfort and complaints in particular from the eyes, the mucous membranes and the skin. In addition it has been debated, wheather a possible long-term risk may be associated with inhalation of even small quantities of respirable fibres.

It has in a recent field study been shown, that the number of children present and their activities during the day in a day-care institution with mineral wool slabs, is of dicisive significance for the mineral fibre content of the indoor air compared to the basic condition during the night hours. In addition it appeared, that variations could be registered from day to day and to the time spend on surface cleaning routines in the institution.

However the number of fibres released from the ceiling surface material made of compressed mineral fibres was less than 1:100 to 1:1000 of the TLV for occupational exposure, and only a small fraction of the total dust and Suspended Particulate Matter.

Testing of MMMF-slabs for release of fibres in a climate chamber and exposure models based on experimental data will be described.

MINERAL PARTICLES IN THE LUNGS OF SUBJECTS RESIDENT IN URBAN AREA - L. Paoletti et al., Istituto Superiore di Sanità, Viale Regina Elena, 299 - 00161 Rome, Italy

We started to investigate the airborne mineral particulate to which a population resident in an urban area is exposed.

This was done by studying the mineral content in lung parenchyma autoptic samples of a group of subjects having lived in an urban area but not having been professionally exposed to dusts. Much importance has been attached to obtaining data on the exposure of the population to asbestos fibers in an urban area and to assessing the type and magnitude of the possible sources of such a pollutant (motor-vehicle traffic, consumer products, etc.) by studying the fiber mineral types.

In the samples studied, up to date a total of seventeen mineral types were identified along with sixteen metal elements in the form of oxides and sulfides.

The frequent observation of tremolite fibers, an amphibolic asbestos type, was remarkable.

It is expected that the collection of a population sample as established by the selection protocol (about 200 subjects), will be completed by 1987.

INFLUENCE OF XENOBIOTICS ON THE TOXICOKINETICS OF TOLUENE IN MAN - M. Wallén, National Board of Occupational Safety and Health, S-171 84 Solna, SWEDEN

Xenobiotics can be expected to influence the toxicokinetics of inhaled, occupationally used, solvents in man. In a series of experimental exposure studies the toxicokinetics of toluene were investigated (1) in coexposure to inhaled p-xylene, (2) in coexposure to simultaneous oral intake of ethanol, (3) in occupationally solvent exposed volunteers, (4) in painters with subjective susceptibility to solvent exposure, and (5) in connection with cigarette smoking.

(1) A mutual decrease in the blood/end-exhaled air concentration ratio was found for toluene and p-xylene when given in combination compared with separate exposure.
(2) The effects of ethanol were a decrease in the total and relative uptake as well as the apparent clearance of toluene and an increase in the toluene concentration in the blood. The solubility of toluene in blood was increased following coexposure to ethanol.
(3) After long term occupational exposure no effects on the uptake and disposition of toluene were seen in painters as compared to a non preexposed group.
(4) When the painters were subdivided into groups with and without high subjective susceptibility to solvent exposure, no differences were observed in the toxicokinetic parameters studied.
(5) Smokers were found to have a smaller elimination rate of toluene after giving up smoking than during their smoking period. The decrease in the apparent clearance was dependent on a smaller total uptake without a corresponding decrease in the blood concentration of toluene.

The toxic effects caused by toluene do not seem to be more adverse by the coexposures with the exception of the acute intake of ethanol. However, altered toxicokinetics of toluene caused by p-xylene or similar compounds or by personal habits such as moking, moderate chronic intake of ethanol, dietary factors, intake of drugs etc have to be considered especially in the case of biological monitoring and risk assessment.

THEORETICAL DEVELOPMENT OF MECHANISM OF CHEMICAL CARCINOGENESIS----- DI-REGION THEORY - Qianhuan Dai,*Center for Chemistry and Bioengineering of Cancer, East Suburb, Beijing Polytechnic University, Beijing, People's Republic of China, 100022.

In China, since 1979 a new conception named Di-region theory related to quantitative structure-carcinogenic activity relationship(QSCAR) and mechanism of chemical carcinogenesis(MCC) has been put forward[1][2], and which has got much encouragement from the international scientific cycles[3]. Based upon a new artificial intelligence strategy of quantum chemical calculation named wholesale molecular orbital calculation(WMO), which is different from the molecule by molecule calculation manner of tradition molecular orbital theory, can obtain all the parameters of a whole compound class, it is discovered that the necessary condition for the carcinogenic activity of polycyclic aromatic hydrocarbons(PAH) is the producing of two reactive centers in its metabolic course, and the favourable distance between both centers approaches characteristically to 2.80-3.00Å, which is just matching with the distance between the pair-wise negative atoms in DNA complementary base pair. Hence the key step of chemical carcinogenesis should be the covalent crosslinking between the DNA complementary base pair, and the mechanism might be the complementary frameshift along the DNA double helix. Based upon the Di-region theory conception and numerous molecular orbital parameters calculated by WMO, by using extrathermodynamics method and/or pattern recognition statistics, QSCAR of parent PAH(49), nonalternant PAH(11) alkyl PAH(187), amino-PAH(65), aza PAH(30), azo dyes(20) and N-nitroso compounds(153),have been established successfully in this laboratory. As yet, all the well-known theories related to carcinogenic mechanism including Pullman's K-region theory, Jerina's Bay-region theory as well as Miller's electrophilic theory all hold monoalkylation viewpoint, and all are faced with difficulties for the establishment of QSCAR. It is surprisely that the specific bifunctional conception of Di-region theory make the puzzling QSCAR of most carcinogen series to become the graspable structure-chemical reactivity relationships. Now, the Di-region theory is being evidenced by metabolic research and other facts, and would be useful for the research on inhalation toxicology. References: [1] Dai Qianhuan,Scientia Sinica(1979),964;English edition(1980),453.[2] Dai Qianhuan,in "Polynuclear Aromatic Hydrocarbons",Cooke et al ed.,1984,p 1045.[3] cf.ES & T, (1984)3, 92A.